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Description

The invention is directed to a method of dispensing liquid into a container, and especially, a method for automatically achieving optimal spacing for such dispensing by the use of pressure feedback.

In some instances in the clinical analysis of blood samples, it is desirable that the patient sample be diluted so as to retest an out-of-range condition. By adding the sample to a diluent, or vice versa, in a predetermined ratio, for example, 1:1, the out-of-range value is reduced to a within-range reading. For example, the condition can occur in assays for glucose.

Prior art approaches have been to eject the sample or the diluent into an empty container until the desired volume is achieved, and then the other liquid is added. In most, if not all of such approaches, no care is given to the location of the bottom of the container. The dispenser tip should not be unduly submerged during liquid ejection, lest substantial amounts of the liquid end up on the surface of the withdrawn tip instead of inside the container. Hence, most such approaches err on the side of spacing the tip so high above the bottom surface of the container that the liquid is ejected in drops, rather than a continuous stream. That is, the distance is too great to allow a continuous stream to flow.

Ejection as drops produces no problem, until the last amount of liquid is ejected. That last amount tends to hang as a pendant drop, with or without perfusion up the outside surface of the dispensing tip. It has been discovered that as much as 25% of the desired volume can end up in such a pendant drop, rather than in the liquid in the container, so that the dilution ratio inside the container can be severely altered. Such a dilution method is unacceptable.

This invention is not the first to appreciate the importance in knowing where the bottom of the receiving container actually is, in each instance. EP-A-0 223 758 teaches the sensing of the bottom of each container, simply by measuring the increase in axial force on the pipette which occurs when it strikes the bottom. However, this technique has a problem in that it is subject to error. For example, if the pipette strikes a side wall or side wall projection of the container before reaching bottom, an axial component of force can still be delivered. This is particularly a problem for non-cylindrical containers or those with sloping side walls. The result in such case can be a false reading of bottoming. Thus, the technique described in EP-A-0 223 758 places an undue premium on proper location of the dispenser tip in the X-Y plane, vis-a-vis the container, to avoid side wall contact. Otherwise, the technique of that application will not in fact always determine the actual bottom. Still further, the axial force on the pipette is measured by this technique using a sensor added only for this purpose. A better technique would use sensors already in place.

It is therefore an object of the present invention to provide a bottom-sensing method that solves the above-mentioned problems.

More specifically, in accordance with the present invention, there is provided a method for dispensing liquid into a container from a dispensing device which can be moved vertically relative to the container by moving means in response to control means and sensing means, the dispensing device having a dispensing orifice which is resiliently mounted in the vertical direction, the method including the steps of:-

a) moving the dispensing orifice vertically towards the bottom of the container,

b) sensing the bottom of the container, and

c) thereafter dispensing liquid from the dispensing device into the container;

characterized in that step a) comprises moving the dispensing orifice to a sealing location beyond the nominal location of the bottom of the container so that the orifice is sealed by the bottom,

and in that step b) comprises the further steps of:-

i) actuating pressure means while the orifice is sealed by a vertical force at the sealing location,

ii) slowly withdrawing the vertical force on the orifice from the container bottom while sensing the pressure on the liquid in the orifice,

iii) detecting a decrease in the pressure when the orifice is no longer sealed against the container bottom and liquid starts to be dispensed from the orifice by the pressure means, and

iv) generating a signal in response to the step iii) which identifies the location of the unsealed orifice as being at the bottom of the container so that all the liquid to be dispensed actually leaves the dispenser.

Therefore, it is an advantageous feature of the invention that the actual bottom, rather than side walls, of each container into which liquid is injected, is sensed to allow proper and complete dispensing of the liquid to be received by the container.

It is another advantageous feature of the invention that a method is provided for injecting liquid into a container from a dispenser which insures, for each container, that all of the liquid ejected from the dispenser is in fact received in the container and is not left on the dispenser.

It is a related advantageous feature of the invention that such a method of injecting liquid is provided which locates the dispenser of the liquid

so that a continuous stream of liquid is provided into the container.

For a better understanding of the present invention, reference will now be made, by way of example only, to the accompanying drawings in which:-

Figures 1A and 1B are partially sectioned, elevational views illustrating a prior art method of injecting liquid into a container;

Figures 2A to 2F are elevational views similar to those shown in Figures 1A and 1B but illustrating the practice of the present invention;

Figure 3 is a partially schematic fragmentary elevational view of apparatus useful in the present invention;

Figure 4 is a profile of the change in pressure which occurs during the process illustrated by Figures 2D and 2E; and

Figure 5 is a flow chart illustrating the steps which are followed in programming an analyzer to carry out the method of the invention.

The invention is hereinafter described in the context of the preferred embodiments, wherein certain preferred dispensing tips are used in a preferred analyzer to dispense liquid, most preferably, patient sample or diluent, into preferred containers in an analyzer such as the type manufactured under the tradename "Ektachem 700" or "Ektachem 250" by Eastman Kodak Company. In addition, the invention is useful regardless of the liquid being dispensed, and the kind of dispensing tip or analyzer that is used. Any container can be used to receive the liquid provided its bottom surface will seal against the dispenser orifice.

The problem addressed by this invention is illustrated in Figures 1A and 1B. That is, a container 10 is located at a station A, to receive a liquid, such as a diluent, from a conventional disposable tip 30, mounted on a dispenser (not shown). To avoid erring on inserting the tip too far into the container so as to ram the tip into the bottom, the analyzer is programmed to err on the "high side", that is, to locate tip 30 an excessive distance "D" above the bottom surface B of container 10. Distance "D" in many cases is too great to allow the injected liquid to pass as a stream. Instead, it passes as drops "d", when a pressure increase $+\Delta P$ is provided, Figure 1A. However, as shown in Figure 1B, the last drop d' is often too small to ensure that it will fall into container 10. Instead, it hangs from tip 30 as a drop d', so that it leaves with the tip (in the direction of arrow 100) (shown in phantom), thus destroying the expected dilution ratio when the patient sample is next injected into the diluent already in the container. That is, the volume of drop d' can be up to 25% of the volume expected to be injected into container 10, which clearly alters the expected dilution ratio.

The method of the invention is best understood from Figures 2A to 2F, using apparatus such as the apparatus shown in Figure 3. That is, a dispenser (not shown in Figures 2A to 2F) has a disposable tip 30 mounted thereon with a dispensing aperture 34, the tip being of any convenient type. (Tips available under the tradename "Ektachem 700" disposable tips from Eastman Kodak Company are useful.)

At a suitable aspirating station, such a tip is filled with an appropriate volume of the liquid having the smaller volume in the mixture, for example, the sample or a diluent such as 10µl of water or 7% bovine serum albumin, plus a "dead" volume, for example, 20µl, and following aspiration, the pressure inside tip 30 is essentially equal to atmospheric (Figure 2A).

Next, the tip is placed vertically over a container, not shown, which is the condition illustrated in Figure 2A. Thereafter, relative movement in the direction of arrow 35, is provided between tip 30 and container 10, Figures 2B and 3. Such relative movement is maintained (preferably by moving tip 30 down towards container 10 fixed on a support 11), until tip 30 seals against bottom surface B, Figure 2C. The dispenser is conventionally constructed to be slightly resilient in at least the vertical direction, thus allowing sufficient over-travel of tip 30 downward against surface B to apply a vertical force without damaging the container or the dispenser, and yet still sealing tip orifice 34 against surface B.

At this point, Figure 2D, the pressure inside tip 30 is increased by an amount +p and the pressure inside tip 30 is monitored by a sensing means. The amount "+p" is that amount just sufficient to eject a meniscus from tip 30 if the tip is not sealed. Thereafter, tip 30 is withdrawn in increments, as shown by arrow 39, until enough of the resilient pressure has been withdrawn, shown as distance Δh, Figure 2E, as to cause tip 30 to unseat and some of the liquid (L) to be ejected onto surface B.

The amount of meniscus which is ejected by pressure increase "+p" depends primarily on the tip geometry. In one example, the pressure +p caused ejection of 5µl of the liquid, but other amounts can be used.

Importantly, while the liquid is ejected, Figure 2E, a pressure decrease -p is registered by the sensing means, and this decrease is used to trigger that the "bottom" (here, surface B) of the container has been reached. This position, shown in Figure 2E, is stored in memory as the "bottom" position.

Thereafter, while tip 30 is withdrawn at a prescribed rate, a new +p' pressure is applied to tip 30 to eject the remaining aliquot of the liquid to be dispensed into this container. That is, the new,

changing height $\Delta h'$ of tip 30 above surface B is selected so as to continue to maintain the ejection of the liquid as a continuous stream, Figure 2F. (Although Figure 2F shows all of the contents of tip 30 being ejected, preferably the above-mentioned dead volume remains.)

Then, when tip 30 is totally withdrawn (not shown), the total distance the dispenser has moved from the tip position shown in Figure 2E is recalled. Thus, knowing the location of surface B as sensed in Figure 2E, the dispenser can re-enter container 10 with a new tip bearing the other liquid of the mixture, and properly locate the new tip at that surface for dispensing the proper aliquot of the other liquid in the manner shown in Figure 2F. That is, knowing where bottom surface B is, the dispenser "knows" where the top of the first liquid is and hence where the new tip should be to dispense the second liquid as a continuous stream. (Conventional software is used to provide such calculations.)

By way of example, Δh of Figure 2E, when liquid L releases out of tip 30 due to the unseating of the tip, can be 0.20mm. The withdrawal of the tip as shown in Figure 2F proceeds with a dispensing pressure sufficient to dispense at a rate of, for example, 100µl/sec.

Suitable analyzer apparatus 20 for carrying out the steps of Figures 2A to 2F is shown in Figure 3. Such an analyzer uses conventional parts, as described for example in US-A-4 794 085. That is, a tip 30 is removably mounted at its larger aperture 32 onto an aspirator/dispenser probe 40. Probe 40 is moved relative to a container 10 suitably supported at 11. That is, probe 40 is moved preferably up and down, by a conventional drive 44. A spring 45 disposed between drive 44 and probe 40 represents the compliancy which allows the drive to "overdrive" tip 30 into container 10 without damage. Probe 40 has an internal passageway 46 connected to a pressure transducer 70 via a hose 52, and also to means 58 for altering the pressure inside tip 30. (Such means 58 comprise, for example, a piston 60 moved inside a cylinder 62 by a drive means 64, between the various positions shown in phantom.)

Control means 80 is used to detect the pressure signal generated by transducer 70, and in turn acts upon both drive means 44 and 64 in accordance with an appropriate program to control the respective movement and pressure of tip 30.

Control means 80 is preferably a microcomputer in analyzer 10, and transducer 70 is one having a high sensitivity, low internal air volume and high stability, for example, a piezoelectric transducer.

Movement of tip 30, in the direction of arrow 35, is in increments, so that aperture 34 moves first a distance y' to the phantom position 30', and then to phantom position 30", and so forth, until the tip has sealed against bottom surface B, also as shown in Figure 2C. A nominal location of surface B can be predicted by a single dry run prior to use, to avoid driving tip 30 too far down against container 10, beyond the resiliency which is built into probe 40.

At this time, an increase in pressure of +p is provided by an advance of piston 60 within cylinder 62 to test for the unseating of tip 30 from bottom surface B. As force on tip 30 is incrementally reduced by drive 44, through the release of spring 45, the pressure inside tip 30 is monitored by transducer 70 plus control means 80 to detect when a sudden decrease occurs which is indicative of the tip becoming unsealed from surface B.

It will be readily appreciated that a threshold signal is set, beyond which the pressure must decrease in amount in order to represent the unsealing of tip 30. For example, if the +p pressure which is used to test for unsealing generates a signal of 450mV, then a useful threshold value is 390mV, where the transducer produces 300mV per 2.54cm of H_2O pressure.

Such a threshold is shown in Figure 4, where a pressure decrease of 400mV occurs at time $T = T_R$, when unsealing first occurs. The remainder of the events shown in Figure 4 are as follows: At point A, liquid is already within the dispensing tip. At point C, the tip is sealed on the bottom. From point C during the time at point D, +p pressure has been applied by the pump (also shown in Figure 2D). The plateau during point E represents the time when the downward vertical force on the tip is gradually reduced (marked "back away"). The pressure drop at T_R represents the unsealing event, and the tip location at this time is "marked". Finally, the pressure rise to point F represents the dispensing of the remainder of the liquid into the container, Figure 2F.

Any suitable program can be used in a conventional manner to program control means 80. The flow chart of Figure 5 is illustrative of the steps of the computing process involved. The process requires, first, that the manual location of bottom surface B be ascertained, step 100, as noted above, to prevent damaging over-travel of the dispenser proble. Next, step 101, the liquid which represents the smaller of the two volumes in the mixture is determined, and it is this liquid, step 102, which is aspirated into a tip 30 on the dispenser. Thereafter tip 30 is advanced into a selected container, step 104, until aperture 34 reaches the nominal location of the bottom surface, where it should seal against bottom surface B, step 106, as determined from step 100.

At this point, the pressure means, namely the piston of the dispenser, is advanced an amount +p, step 108, while the pressure is monitored via the transducer (70 in Figure 3). This accomplishes two things, namely, it confirms that indeed the tip is sealed. Also, it allows tip 30 to be thereafter withdrawn a selected single increment, step 110, which for example can be six half-steps if drive 44 of Figure 3 is a stepper motor. Control means 80 then queries, step 112, whether the pressure in tip 30 has decreased more than the selected threshold. If not, step 110 is iterated until the query is answered positively, step 114. At this point, the "location", that is, the position of drive 44, is stored in memory, and the pressurizing means is actuated to generate a +p' to further eject the remaining amount of the desired aliquot of diluent, step 116, while tip 30 is incremented backwards by drive 44 at a prescribed rate.

Finally, tip 30 is withdrawn from the container, step 118.

Thereafter, as a further option, a new tip is provided with the liquid having the larger volume in the mixture, step 120, the tip is advanced to the predicted location of the liquid surface previously deposited, step 122, as determined by step 114, and the second liquid is injected into the first, step 124. Steps 120 to 124 are considered optional, since once the first liquid is in place, other steps can be followed with respect to that liquid or even in properly locating a new tip with the second liquid, relative to the surface of the first liquid.

Claims

1. A method for dispensing liquid into a container from a dispensing device which can be moved vertically relative to the container by moving means in response to control means and sensing means, the dispensing device having a dispensing orifice which is resiliently mounted in the vertical direction, the method including the steps of:-

   a) moving the dispensing orifice vertically towards the bottom of the container,
   b) sensing the bottom of the container, and
   c) thereafter dispensing liquid from the dispensing device into the container;

   characterized in that step a) comprises moving the dispensing orifice to a sealing location beyond the nominal location of the bottom of the container so that the orifice is sealed by the bottom,

   and in that step b) comprises the further steps of:-

   i) actuating pressure means while the orifice is sealed by a vertical force at the sealing location,
   ii) slowly withdrawing the vertical force on the orifice from the container bottom while sensing the pressure on the liquid in the orifice,
   iii) detecting a decrease in the pressure when the orifice is no longer sealed against the container bottom and liquid starts to be dispensed from the orifice by the pressure means, and
   iv) generating a signal in response to the step iii) which identifies the location of the unsealed orifice as being at the bottom of the container so that all the liquid to be dispensed actually leaves the dispenser.

2. A method according to claim 1, wherein step b) further includes labeling the location of the unsealed orifice as the "bottom" location, and thereafter continuing the dispensing of liquid into the container while withdrawing the orifice from the container bottom and tracking the distance traveled away from the "bottom" location.

3. A method according to claim 1 or 2, wherein the dispensing orifice is part of a clinical analyzer and the liquid is a diluent for a patient sample.

Patentansprüche

1. Verfahren zur Abgabe einer Flüssigkeit aus einer Abgabevorrichtung in einen Behälter, wobei die Abgabevorrichtung relativ zum Behälter in Reaktion auf eine Steuereinrichtung und eine Erfassungseinrichtung durch eine Bewegungseinrichtung vertikal bewegt werden kann, und wobei die Abgabevorrichtung eine Abgabeöffnung aufweist, die in vertikaler Richtung nachgiebig angebracht ist, wobei das Verfahren die Schritte

   a) des Bewegens der Abgabeöffnung vertikal zum Boden des Behälters,
   b) des Erfassens des Bodens des Behälters, und danach
   c) des Abgebens der Flüssigkeit aus der Abgabevorrichtung in den Behälter umfaßt;

   dadurch **gekennzeichnet**, daß der Schritt a) das Bewegen der Abgabeöffnung in eine verschließende Stellung jenseits der nominalen Position für den Boden des Behälters beinhaltet, so daß die Abgabeöffnung durch den Boden dicht verschlossen ist,

   und daß der Schritt b) die weiteren Schritte
   i) des Betätigens einer Druckeinrichtung, während die Abgabeöffnung durch eine vertikale Kraft in der verschließenden Stellung verschlossen ist,

ii) des langsamen Wegnehmens der vertikalen Kraft auf die Abgabeöffnung am Behälterboden, während der Druck auf die Flüssigkeit in der Öffnung erfaßt wird,

iii) des Erfassens der Abnahme des Drucks, wenn die Abgabeöffnung nicht mehr durch den Behälterboden verschlossen ist und die Flüssigkeit beginnt, durch die Druckeinrichtung aus der Abgabeöffnung abgegeben zu werden, und

iv) des Erzeugens eines Signals in Reaktion auf den Schritt iii) umfaßt, wodurch die Stellung der nicht verschlossenen Abgabeöffnung als am Boden des Behälters befindlich festgestellt wird, so daß die ganze abzugebende Flüssigkeit die Abgabevorrichtung tatsächlich verläßt.

2. Verfahren nach Anspruch 1, wobei der Schritt b) des weiteren das Markieren der Position der nicht mehr verschlossenen Abgabeöffnung als die "Boden"-Position und danach das Fortführen der Abgabe der Flüssigkeit in den Behälter umfaßt, während die Abgabeöffnung vom Behälterboden zurückgezogen wird und der von der "Boden"-Position weg zurückgelegte Weg verfolgt wird.

3. Verfahren nach Anspruch 1 oder 2, wobei die Abgabeöffnung Teil eines klinischen Analysegeräts ist und die Flüssigkeit ein Verdünner für eine Patientenprobe.

Revendications

1. Procédé de distribution de liquide dans un conteneur depuis un dispositif de distribution qui peut être déplacé verticalement par rapport au conteneur par un moyen de déplacement en réponse à un moyen de commande et à un moyen de détection, le dispositif de distribution comportant un orifice de distribution qui est monté de façon élastique suivant la direction verticale, le procédé incluant les étapes de :

a) déplacement de l'orifice de distribution verticalement en direction du fond du conteneur ;

b) détection du fond du conteneur ; et

c) distribution du liquide ensuite depuis le dispositif de distribution dans le conteneur,

caractérisé en ce que l'étape (a) comprend le déplacement de l'orifice de distribution jusqu'à un emplacement d'étanchéité au-delà de l'emplacement nominal du fond du conteneur de telle sorte que l'orifice soit rendu étanche par le fond et en ce que l'étape (b) comprend les autres étapes de :

i) actionnement d'un moyen de pression tandis que l'orifice est rendu étanche par une force verticale au niveau de l'emplacement d'étanchéité ;

ii) retrait lent de la force verticale appliquée sur l'orifice depuis le fond du conteneur tout en détectant la pression exercée sur le liquide dans l'orifice ;

iii) détection d'une diminution de la pression lorsque l'orifice n'est plus rendu étanche vis-à-vis du fond du conteneur et qu'un liquide commence à être distribué depuis l'orifice par le moyen de pression ; et

iv) génération d'un signal en réponse à l'étape (iii), lequel identifie l'emplacement de l'orifice non rendu étanche comme étant le fond du conteneur de telle sorte que la totalité du liquide à distribuer quitte réellement le distributeur.

2. Procédé selon la revendication 1, dans lequel l'étape (b) inclut en outre l'étiquetage de l'emplacement de l'orifice non rendu étanche en tant qu'emplacement "de fond" puis la poursuite de la distribution du liquide à l'intérieur du conteneur tout en retirant l'orifice du fond du conteneur et en suivant la distance parcourue depuis l'emplacement "de fond".

3. Procédé selon la revendication 1 ou 2, dans lequel l'orifice de distribution est une partie d'un analyseur clinique et le liquide est un diluant pour un échantillon d'un patient.

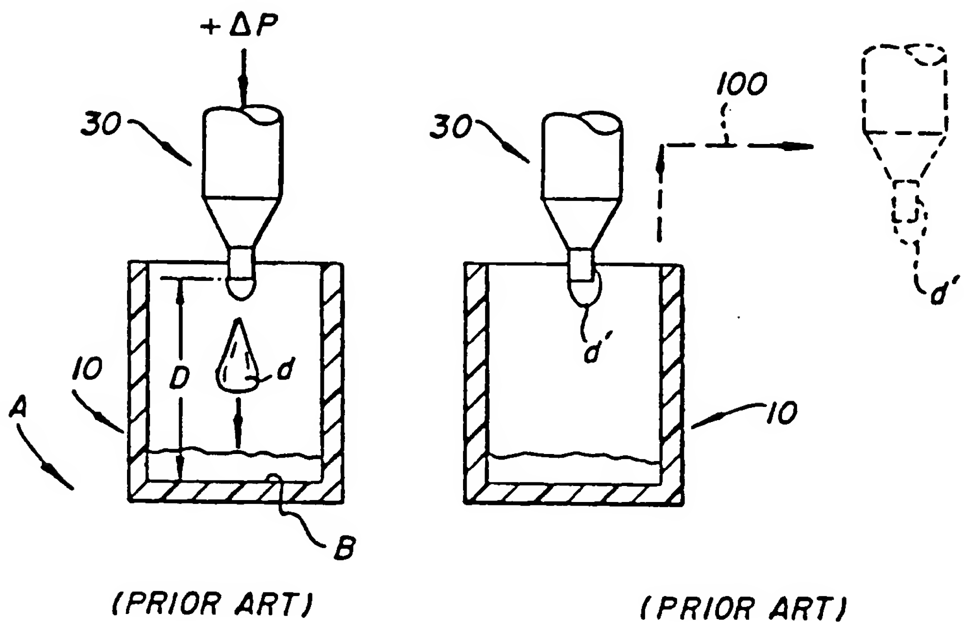

Fig. 1A

Fig. 1B

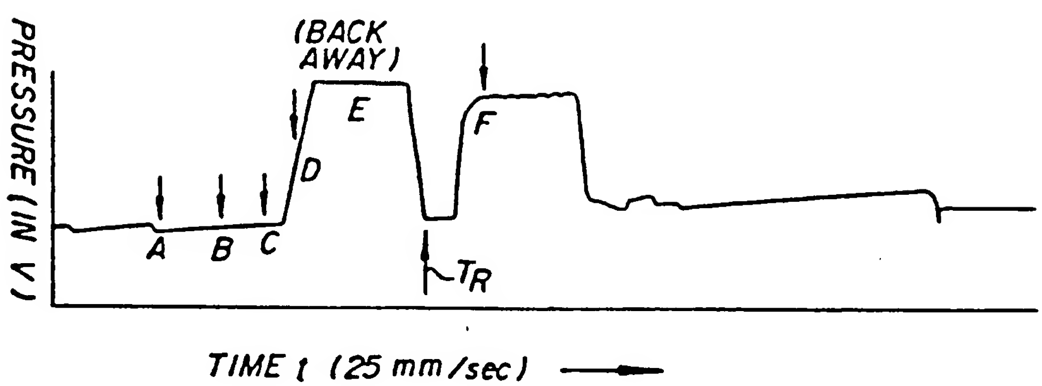

Fig. 4

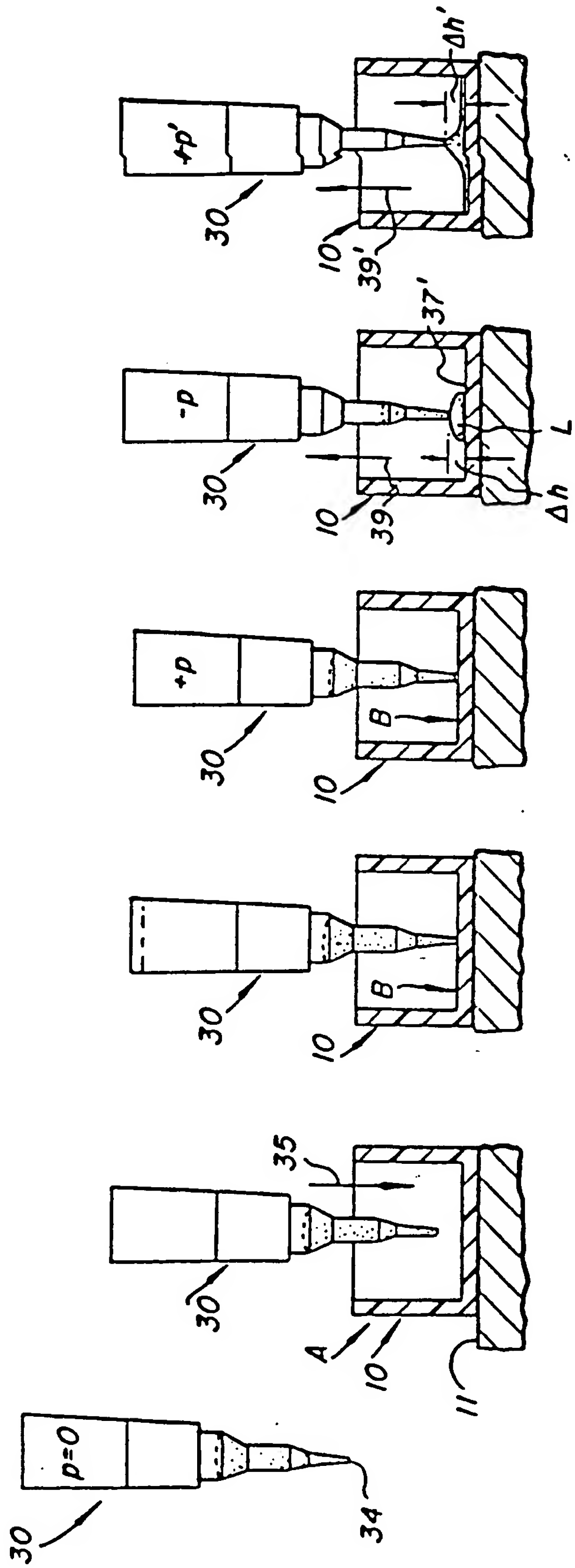

Fig. 2A

Fig. 2B

Fig. 2C

Fig. 2D

Fig. 2E

Fig. 2F

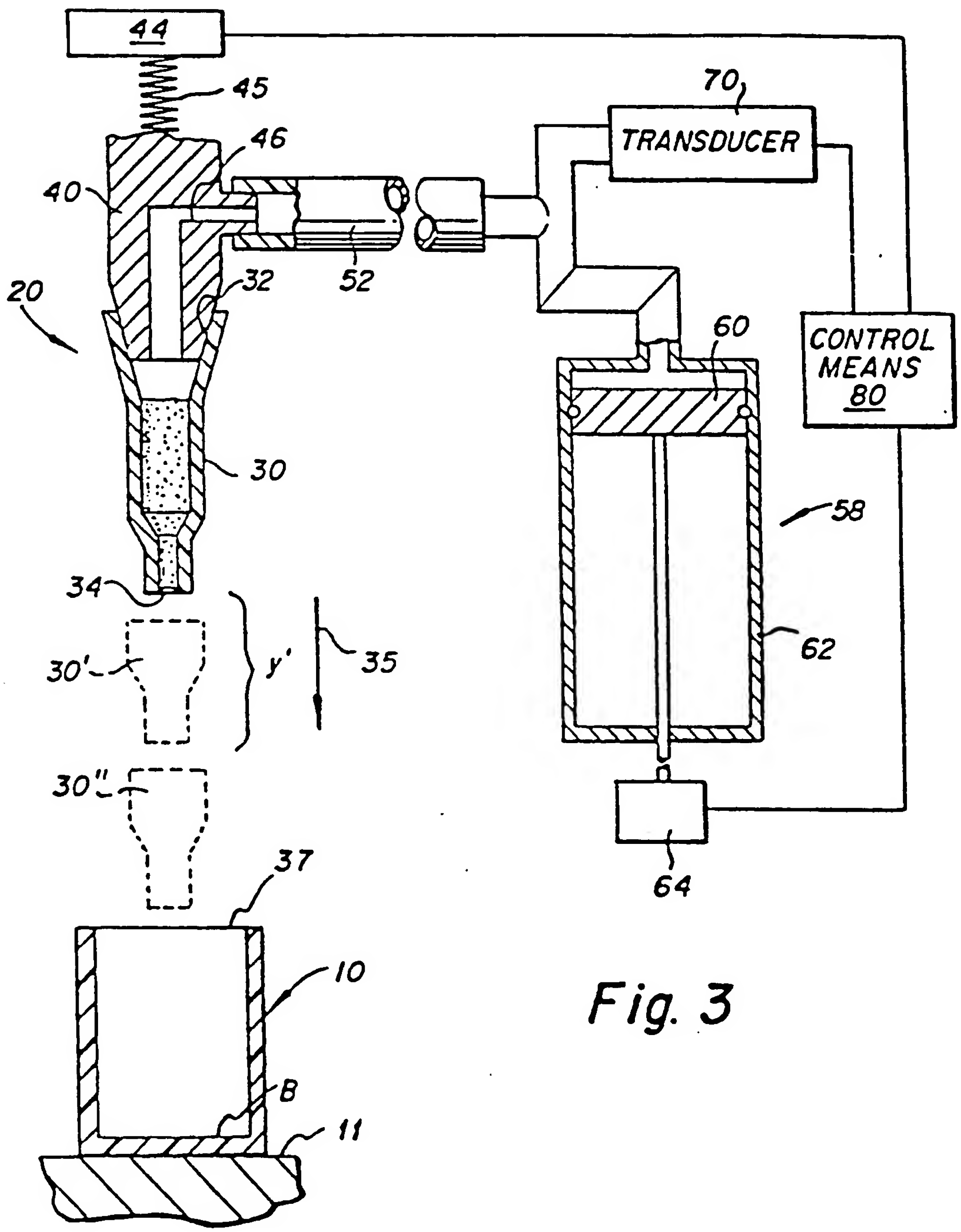
44
45
46
40
20
32
52
70
TRANSDUCER
60
CONTROL MEANS 80
30
58
34
30'
y'
35
62
30"
64
37
10
B
11

Fig. 3

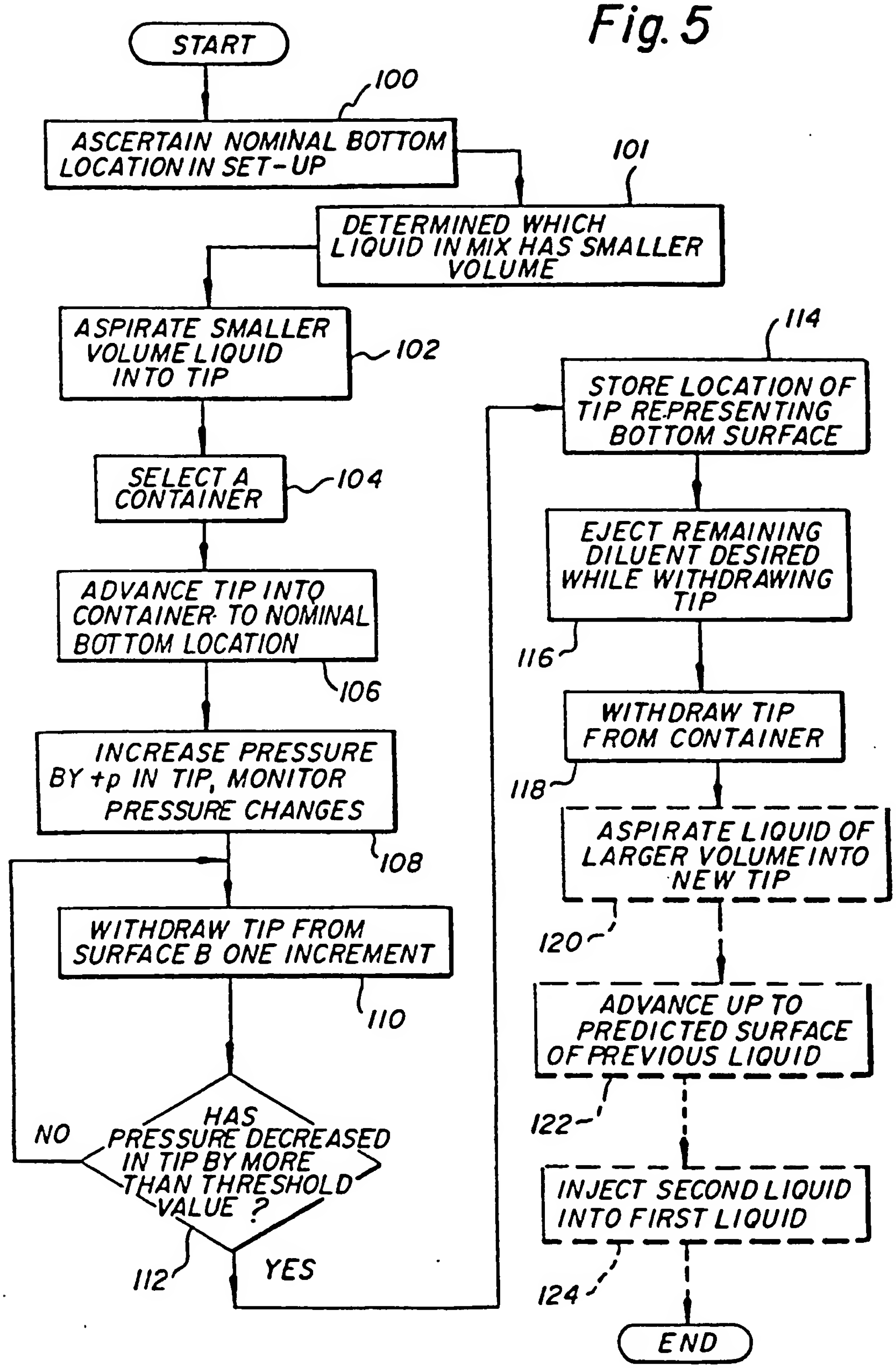
START
ASCERTAIN NOMINAL BOTTOM LOCATION IN SET-UP
100
DETERMINED WHICH LIQUID IN MIX HAS SMALLER VOLUME
101
ASPIRATE SMALLER VOLUME LIQUID INTO TIP
102
SELECT A CONTAINER
104
ADVANCE TIP INTO CONTAINER TO NOMINAL BOTTOM LOCATION
106
INCREASE PRESSURE BY +p IN TIP, MONITOR PRESSURE CHANGES
108
WITHDRAW TIP FROM SURFACE B ONE INCREMENT
110
HAS PRESSURE DECREASED IN TIP BY MORE THAN THRESHOLD VALUE ?
112
NO
YES
STORE LOCATION OF TIP REPRESENTING BOTTOM SURFACE
114
EJECT REMAINING DILUENT DESIRED WHILE WITHDRAWING TIP
116
WITHDRAW TIP FROM CONTAINER
118
ASPIRATE LIQUID OF LARGER VOLUME INTO NEW TIP
120
ADVANCE UP TO PREDICTED SURFACE OF PREVIOUS LIQUID
122
INJECT SECOND LIQUID INTO FIRST LIQUID
124
END

Fig. 5